



Europäisches Patentamt
European Patent Office
Office européen des brevets



Publication number:

0 361 677 B1

12

EUROPEAN PATENT SPECIFICATION

- 45 Date of publication of patent specification: **24.11.93** 51 Int. Cl.⁵: **A61K 47/30**, C11D 17/00,
A01N 25/10
- 21 Application number: **89308606.6**
- 22 Date of filing: **24.08.89**

54 **Polymeric compositions and methods of producing them.**

30 Priority: **24.08.88 GB 8820061**
24.08.88 GB 8820062
19.01.89 GB 8901194

43 Date of publication of application:
04.04.90 Bulletin 90/14

45 Publication of the grant of the patent:
24.11.93 Bulletin 93/47

84 Designated Contracting States:
BE CH DE FR GB GR LI NL SE

56 References cited:
EP-A- 0 102 265
EP-A- 0 290 807
US-A- 3 584 113

73 Proprietor: **ALLIED COLLOIDS LIMITED**
P.O. Box 38,
Low Moor
Bradford, West Yorkshire BD12 0JZ(GB)

72 Inventor: **Langley, John**
4 Wharfedale Gardens
Baildon
Shipley West Yorkshire BD17 6TM(GB)
Inventor: **Symes, Kenneth Charles**
4 Silk Mill Drive
East Morton
Keighley West Yorkshire BD20 2UU(GB)

74 Representative: **Lawrence, Peter Robin**
Broughton et al
GILL JENNINGS & EVERY,
Broadgate House,
7 Eldon Street
London EC2M 7LH (GB)

EP 0 361 677 B1

Note: Within nine months from the publication of the mention of the grant of the European patent, any person may give notice to the European Patent Office of opposition to the European patent granted. Notice of opposition shall be filed in a written reasoned statement. It shall not be deemed to have been filed until the opposition fee has been paid (Art. 99(1) European patent convention).

Description

It is well known to formulate an active ingredient (for instance an agricultural or pharmaceutical active material or a detergent enzyme) in the form of particles using a polymeric binder. For instance the active ingredient may be distributed through a polymeric matrix which, in practice, generally contains a relatively large amount of inert filler.

If the binder is water soluble, ambient atmospheric moisture will readily permeate into the particles, and addition of the particles to water will result in rapid release of the active ingredient. There are many instances where it is desirable that, for instance, release should only occur when the particles are exposed to a predetermined pH environment and it is standard practice to apply a polymeric coating around the particles, the polymer being impermeable at one pH and permeable (or soluble) at another pH. Such coatings are, for instance, widely used as enteric coatings. An example is in WO88/06407 wherein the particles of a fungal active ingredient distributed in a matrix are provided with an enteric polymeric coating that will permit release of the fungus only at a predetermined pH. Another example is in EP-A-277532.

A problem with enteric coatings is that there is a risk that they may not provide an adequate barrier over the total area of every granule or tablet, either because of non-uniformity in the coating or because they are accidentally fractured after application. Thus active ingredient near the outside of the matrix is liable to be exposed to ambient conditions. When the matrix itself is accidentally fractured (as frequently happens due to the relatively low amount of protective polymer that is usually included in the matrix) then this results in exposure of further active ingredient to ambient conditions. Another problem arises when it is necessary to combine rapid release upon addition of the particles to suitable water with the need for thorough protection for the active ingredient from the ambient atmosphere during storage. For instance particles containing an enzyme for a detergent need to dissolve very rapidly upon the addition to wash liquor but need to prevent deactivation of the active ingredient (by migration of atmospheric moisture through the particles) during storage. If the protective outer coating is sufficiently impermeable to prevent deactivation of the enzyme by ambient moisture then the particles are liable to dissolve only very slowly, while if the coating is sufficiently thin that the particles will dissolve fast then the coating is liable to provide an ineffective barrier to atmospheric moisture.

Additionally, it is undesirable to have to make the particles in two stages, the initial stage involving the formation of the matrix and the second stage involving the application of the protective coating to it.

Various ways are known for forming the initial matrix containing the active ingredient and around which the coating can be applied. For instance biologically produced active ingredients can typically be put into particulate form by spray drying a fermentation broth and aggregating the resultant powder using a polymeric binder that typically is soluble in water.

It would be desirable to be able to provide particles containing active ingredient wherein the particles give good protection to the active ingredient during storage of the particles (even if the particles are fractured) and yet will permit very rapid exposure of the active ingredient to different ambient conditions, for instance exposure to alkaline water.

In GB 1,353,317 an enzyme is precipitated from its solution by the addition of a relatively very small amount of anionic polymer, followed by collection of the resultant precipitate and drying. However the amount of polymer would be much too low to protect the enzyme or control its release.

In U.S. 3,584,113 particles comprising a water insoluble resin containing a medical ingredient are made by spray drying, and the resin may be introduced as an ammonium salt wherein ammonia is split off during the spray drying.

It would be desirable to be able to provide a simple method of providing particles comprising active ingredient substantially uniformly distributed through a matrix of polymeric material that is relatively insoluble and non-swellable in water at pH above 7 but that can be solubilised by exposure to a higher pH.

The invention provides a process of forming a particulate composition comprising particles comprising an active ingredient distributed substantially uniformly through a dried matrix comprising anionic polymeric material wholly or mainly in free acid form, wherein the amount of polymeric material in the particles is at least 0.5 times the weight of active ingredient and is at least 50% of the weight of the matrix, the polymeric material is soluble or swellable in water at a solubilising pH above 7, and the polymeric material at least in the outer surface of the matrix is substantially less soluble or less swellable in water at a pH below the solubilising pH, characterised in that the process comprises forming a dispersion in water immiscible liquid of aqueous particles containing a solution or dispersion of the active ingredient either in an aqueous solution of a salt of the polymer with a volatile amine or in an oil-in-water emulsion of the polymer wholly or mainly in free acid form, and subjecting the dispersion to azeotropic distillation and thereby forming the particles comprising the active ingredient distributed substantially uniformly through a dried matrix comprising the

anionic polymeric material wholly or mainly in free acid form.

The polymer in the particles includes carboxylic or other suitable anionic groups wholly or mainly in free acid form and the polymer can subsequently be rendered more soluble in water by converting them to alkali metal or amine salt form.

5 The process of the invention provides a convenient way of achieving either a stable dispersion of particles below 10 μ m or beads of particles above 30 μ m.

The particles obtained in the invention have a number of advantages. One advantage is that the protection and release properties are provided by the use of the matrix polymer itself, and so it is not necessary to subject the particles to a separate coating step. Another advantage is that, since it is
10 unnecessary to provide an enteric coating, it does not matter if the particles are subjected to friction or other forces that would be liable to fracture the protective coating that, prior to the invention, would have been provided around the matrix. Another advantage is that, if the particles are fractured, the high polymer content means that only a relatively small amount of the active ingredient will be exposed to the ambient conditions. Naturally, improved results are achieved, from this point of view, when the amount of polymer is
15 well above the minimum specified above. As explained below the amount of polymer is generally at least 7 times the amount of active ingredient and the polymer generally constitutes at least 90% of the matrix.

In addition to requiring the use of this unusually large amount of polymer, the invention also requires that the polymer shall have been introduced in one of two forms.

In one form the polymer is initially introduced as a solution of a water soluble salt with a volatile amine
20 of a polymer that is relatively insoluble and non-swelling in acid and throughout which the active ingredient is dispersed or dissolved, and the solution is heated to form the dry matrix and to volatilise the amine and thereby form a polymer that is insoluble in acid. The preferred volatile amine is ammonia.

In another form, the polymer is initially introduced as an emulsion of film forming polymeric material throughout which the active ingredient is substantially uniformly dispersed or dissolved and the emulsion is
25 then dried to form the dry matrix, the polymeric material being film forming at the drying temperature or at a lower temperature. The aqueous polymer phase that is dispersed in the non-aqueous liquid is itself an emulsion of polymer in water.

The final matrix is homogeneous in the sense that the polymeric material provides a continuous phase throughout the matrix. This minimises the risk of fracture of beads or tablets of the composition. Generally
30 the polymeric material constitutes at least 50%, preferably at least 75% and most preferably at least 90% by weight of the solid composition formed of the matrix, active ingredient and any inert material distributed through the matrix.

The amount of polymeric material must be sufficient to form the matrix and is preferably at least twice the amount (by weight) of active ingredient. Generally it is at least 7 times and usually at least 10 times the
35 amount of active ingredient. It is usually unnecessary for it to be more than 50 times the amount of active ingredient and suitable amounts are generally in the range 15 to 30 times the amount of active ingredient. As a result of having this relatively large polymeric content, the active ingredient is present in a relatively dilute state within the matrix and so if there is any physical damage to the matrix the amount of active ingredient that is exposed to the environment is low.

The active ingredient can be included in a solution or emulsion of monomeric material that is then polymerised, in the presence of the active ingredient, to form the solution or emulsion of film forming
40 polymeric material. Preferably however the polymer is provided as a solution or emulsion and the active ingredient is then combined with this preformed polymer solution or emulsion. The active ingredient can be dissolved or dispersed into the polymer solution or emulsion. The active ingredient must be distributed
45 substantially uniformly through the solution or emulsion (and through the final matrix).

The polymer that is used should be film forming in the sense that the polymeric residue forms, during the process, a coherent mass of dry polymeric material when the solvent is removed from the solution or the continuous phase is removed from the emulsion. The glass transition temperature should therefore preferably be at or below the chosen distillation temperature and often it is below 40°C, frequently below
50 20°C.

At this stage of the process, the polymer can be insoluble in water in which event it is present as an emulsion that has been made by oil-in-water emulsion polymerisation. The emulsion should be such that the polymer particles are film forming, as described above, and if necessary the emulsion may include a plasticising additive that will render the polymer film forming. For instance a solvent or plasticiser for the
55 polymer may be included in the emulsion in an amount sufficient to render the emulsion particles film forming.

When the polymer is present as an emulsion it may be a polymer that is cross linked sufficiently for the final matrix to be insoluble in all aqueous media but to be swellable in aqueous media of selected pH. Often

however the polymer is linear and so is potentially soluble in aqueous media at selected pH values.

Suitable emulsion polymers are made by oil-in-water emulsion polymerisation of one or more ethylenically unsaturated monomers that are insoluble in the water phase of the polymerisation mixture. The monomers that are emulsion polymerised are a blend of anionic solubilising monomers and non-ionic monomers, the overall blend being insoluble at the pH of the emulsion. The emulsion polymerisation is conducted at a pH below 7 at which the monomer blend and the polymer is insoluble and non-swellable. The amount of solubilising ionic monomer will be such that the final polymer can be solubilised by exposure to the chosen alkaline pH but not at a lower pH.

The other monomers in the blend are non-ionic and have a solubility such that the blend is insoluble at the pH of the emulsion. They can include water soluble monomers such as (meth) acrylamide but generally they are all water insoluble monomers such as alkyl (meth) acrylates, styrene, acrylonitrile, vinyl chloride, vinyl acetate or vinyl butyl ether. Ethyl acrylate is preferred.

Suitable anionic monomers are ethylenically unsaturated carboxylic or sulphonic monomers, most preferably monomers such as (meth) acrylic acid, crotonic acid, itaconic acid, maleic acid, (meth) allyl sulphonic acid, vinyl sulphonic acid and 2-acrylamido-2-methyl propane sulphonic acid. Methacrylic acid is preferred.

The polymer is often formed from 10-70% methacrylic acid or other anionic monomer, 10-70% ethyl acrylate or other insoluble monomer and 0-70% acrylamide or other soluble non-ionic monomer.

Instead of the polymer being an emulsion at the time of incorporation of the active ingredient, the polymer can be an aqueous solution of a polymer that has been solubilised by volatile amine (preferably ammonia) and the amine is volatilised by heating the polymer during drying.

Thus an oil-in-water emulsion polymer containing acrylic acid or other anionic monomer may be converted into a solution by adding ammonia or other volatile amine and the polymer then converted back to a water-insoluble form by heating to drive off the ammonia. This is desirable when the polymer is to prevent release of the active ingredient except when the particles are exposed to external predetermined pH conditions. However when the purpose of putting the polymer into a less soluble form is primarily to reduce the hydrophilicity of the particles then it is unnecessary to start with an oil-in-water emulsion polymer. Instead, the polymer can be a polymer that has some degree of water solubility at pH below 6 (for instance polyacrylic acid) but which is much more soluble and hydrophilic when the carboxylic acid groups are neutralised.

In these circumstances, the polymer is a polymer of a water soluble monomer or monomer blend, generally being formed from anionic monomer as described above either alone or with water soluble non-ionic monomer, such as methacrylamide. Preferred polymers are formed from 50 to 100% (meth) acrylic acid and 0 to 50% acrylamide. Products made in this manner are of particular value when the active ingredient is a detergent enzyme since the partial or fully free acid form of the polymer is much less hydrophilic than the full salt form of the polymer and so gives better protection against ambient moisture during storage, but the polymer dissolves rapidly in wash liquor containing detergent, especially because such liquor is usually slightly alkaline.

The molecular weight of the water soluble polymer will be selected having regard to the concentration and solution viscosities that are required and, especially, the gel strength that is required in the final beads. If the molecular weight is too high in a solution polymer it can be difficult to form a stable dispersion of aqueous polymer particles containing a commercially useful concentration of active ingredient and so for many polymers the molecular weight should be below 1 million, often below 500,000. However higher molecular weights can easily be used when the polymer is an emulsion polymer. If the molecular weight is too low the final gel strength may be inadequate, even if the beads do have surface cross linking.

The polymers that are used in the invention may be unreactive polymers, i.e., polymers that cannot undergo any significant chain extension even though it may be possible to cause cross linking through pendant groups since any such cross linking does not usually result in any significant exotherm or other conditions that might damage the active ingredient. It is also possible to use a polymer that undergoes chain extension by addition polymerisation during the process provided this does not involve the presence of deleterious amounts of initiator, exotherm or other conditions that might damage the active ingredient. The risk of this can be minimised by ensuring that the reactive polymer already has a substantial chain length, for instance at least 50 and usually at least 100 carbon atoms in the chain. Depending upon the degree of unsubstitution in the reactive polymer, the final polymer may be linear or may be cross linked and, if cross linked, the polymeric matrix will then be swellable rather than soluble. Preferred reactive polymers are described in EP-A-0328321.

The polymer may undergo cross linking before, after or preferably during its conversion to dry particles. For instance it is known that many polymers, especially those containing anionic groups, can undergo ionic

cross linking if exposed to polyvalent metal compounds and so the inclusion of such compounds in the aqueous solution of polymer or in the non-aqueous liquid or both can result in cross linking. If the polyvalent metal compound is preferentially soluble in the non-aqueous liquid (for instance being aluminium isopropoxide or other polyvalent metal alkoxide) then the cross linking will be concentrated primarily at the surface of the particles. If the cross linking agent is preferentially soluble in the aqueous solution of polymer then the cross linking may occur substantially uniformly throughout the particles. Cross linking agents such as glutaraldehyde can be used with appropriate polymers. By appropriate selection of the type and amount of cross linking it is possible to control the physical properties of the particles. For instance it is possible to control the release of active ingredient from the particles and/or to increase the gel strength of the particles and/or to increase the hardness, or reduce the stickiness, of the surface of the particles. Also, if the cross linking is concentrated on the surface of the particles, the resultant particles tend to dissolve more rapidly into water.

In order to form the desired particles, the active ingredient is combined with the polymer solution or emulsion so as to form an aqueous phase containing the polymer and the active ingredient distributed substantially uniformly throughout the aqueous phase.

The concentration of the polymer in the aqueous composition containing polymer and active ingredient will depend on the viscosity of the solution or emulsion but is generally in the range 5 to 50%, typically 20 to 30%.

The active ingredient can be provided in solid form that is dispersed or dissolved into the polymer solution or emulsion or it can be provided in liquid form, for instance as an aqueous solution or emulsion. In particular, when it is a biologically produced material, it can be provided in the form of a fermentation liquor or plant extract containing the material, as described in EP-A-0356240. The aqueous phase can contain pigments, fillers or stabilisers, if required. For instance polyhydroxy compounds such as sucrose or propylene glycol can be introduced as stabilisers for enzymes.

The immiscible liquid is normally a water immiscible liquid that consists of or includes an appropriate hydrocarbon or other water immiscible, organic solvent that will form an azeotrope with water. The azeotroping is preferably conducted at temperatures below 100 °C and if the active ingredient is sensitive to elevated temperatures the azeotroping is preferably conducted under reduced pressure using a solvent such that the maximum temperature to which the dispersed particles are subjected is not more than 80 °C and preferably is always kept below 70 °C and preferably below 50 °C, for instance as low as 30 °C. Sodium sulphate or other suitable salt may be added to lower the necessary azeotroping temperature.

When the solution or emulsion is dispersed into an immiscible liquid, dispersion may be facilitated by the presence of a water-in-oil emulsifier and/or by the presence of an amphipathic polymeric stabiliser, for instance formed from hydrophilic and hydrophobic acrylic monomers. Suitable immiscible liquids, emulsifiers and stabilisers for this purpose are those that are conventional in reverse phase polymerisation and are described in for instance EP-A-128661 and EP-A-126528. The stabilisers described in GB 2,002,400 or, preferably, GB-A-2,001,083 or GB-A-1,482,515 are particularly preferred. If a polymer emulsion is being dispersed then the emulsifier that is used must not be such as to cause breakage of the polymer-in-water emulsion.

The particle size of the aqueous droplets and the final particles can be controlled by choice of the amount of shear to which the dispersion is subjected, choice and amount of stabiliser and choice and amount of surfactant. When the end product is to be a stable dispersion in oil or other immiscible liquid it is preferred to use a water-in-oil emulsifier to promote the formation of small particles having a size below 10 μm, for instance below 3 μm. However when beads are required surfactant can be omitted and it is possible to make, for instance, beads having a size of at least 30 μm, generally at least 80 μm, preferably in the range 100 to 500 μm, although larger particles up to 1 or 2 mm can be provided.

The invention is of particular value when applied to the formation of beads. When making the beads by azeotroping, the azeotroping is continued until the particles are sufficiently dry that they can be recovered from any residual immiscible liquid, for instance by conventional centrifuging or other filtration techniques. The particles can then be further dried if desired by extraction with acetone or other suitable organic liquid or, preferably, by exposure to warm air, generally as a fluidised bed.

The active ingredient may be any material that is required to be releasably trapped within a polymeric matrix and thus may be selected from synthetically produced materials, for instance, finely divided pigment, agriculturally active pesticides and other chemicals, and pharmaceutically active chemicals, and biologically-produced materials such as enzymes, fungi, spores, bacteria, cells and antibiotics. The invention is of particular value when the active ingredient is one that would interfere with or be damaged by monomer from which the polymer is made or would tend to be deactivated (either by evaporation or desensitisation) if exposed to exothermic polymerisation. The invention is therefore of particular value when

the active ingredient is a sensitive material that is liable to be desensitised.

One particularly preferred type of active ingredient is a protease, especially an alkaline protease, of the type used in detergents, but other suitable enzymes for washing powders include amylases and lipases. For instance beads made by the invention can be included in washing powders and dispersions made by the invention can be included in liquid detergents.

Another active ingredient is a biologically active material that is to be protected from the acid pH that prevails in the stomach and which is to be released at the higher pH that prevails in the lower gastro intestinal tract. Although this can be an active ingredient that exerts an effect in the human or livestock through which it is passing, the active ingredient is preferably a biopesticide, bioherbicide or biofertiliser. An example is *Bacillus Thuringiensis* toxin for killing larvae. With this, and with many other microbial products, the cells can be encapsulated either dead or alive because it is the toxic protein within the cell, rather than the living cell that is required. However in some instances it is desirable for the cell to be alive within the polymeric matrix in order that it can metabolise and multiply as soon as it is released from the matrix, for instance on a leaf surface, in the ground, or at some point in the alimentary canal.

The invention is of particular value when the active ingredient is an active ingredient that is to exert a pesticidal effect in the faeces of livestock since it is possible to formulate the polymeric matrix such that there is no release of the active ingredient as it passes through the animal but that there is release due to the exposure to ammonia that is formed in the faeces after they have been deposited by the livestock.

Thus an important aspect of the invention is the incorporation of a veterinary pesticide in a polymeric matrix that does not swell or dissolve when exposed to the pH conditions in the mouth (that can be close to pH 7) or elsewhere as it passes through the body of the animal or fowl but which is solubilised or swollen upon exposure to the ammonia that is formed by natural degradation of the faeces after being deposited in the field or elsewhere. This is of value for killing or controlling flies and other insects that tend to feed on faeces and, in particular, for killing nematodes. Thus the active ingredient can be a fungal material of a nematode-destroying fungus, as discussed in WO88/06407.

The following are examples.

Example 1

A copolymer of ethyl acrylate and methacrylic acid is made by oil-in-water emulsion polymerisation to a medium molecular weight and the polymer is dissolved in aqueous ammonia to give a 20% solution. The active ingredient is dissolved or suspended in this solution in a polymer:active ingredient ratio by weight of 19:1.

The solution is stirred into a paraffinic oil in the presence of an amphipathic polymeric stabiliser formed from stearyl methacrylate, methyl methacrylate and methacrylic acid. The resultant dispersion is subjected to azeotropic distillation under reduced pressure such that the maximum temperature in the dispersion does not exceed about 50 °C. The ammonia is driven off during this distillation to render the polymer insoluble in water. Once sufficient water has been taken off for the dispersed particles to be substantially dry to touch, they are separated from the remaining liquid by filtration and can then be further dried in conventional manner. They have a particle size in the range 100 to 1,000 μm.

The resultant beads, when exposed to acidic conditions (for instance typical of those prevailing in the stomach) remain wholly unswollen and give substantially no release of the active ingredient. However when the beads pass into an area of higher pH, for instance as they pass further down the alimentary canal, they swell to start releasing their active ingredient and eventually or immediately dissolve totally. The active ingredient is *Bacillus Thuringiensis*.

Example 2

A solution is formed of 640g 25% emulsion at pH 4 of a copolymer of methacrylic acid and butyl acrylate and 160g 5% detergent protease solution (i.e., 8g dry weight enzyme and 160g dry weight polymer) and its pH is adjusted to 7. 1600g of a water immiscible liquid (solvent 41) and 53g of a 15% solution inorganic solvent of an amphipathic polymeric stabiliser are charged to a 3 litre resin pot equipped with a mechanical stirrer and a Dean & Stark apparatus connected to a condenser and the aqueous phase is added and the mixture stirred for five minutes, leading to the formation of small bead droplets. The contents are then warmed to the chosen temperature, typically 45 °C, and solvent and water azeotropically distilled by reducing the pressure to a value at which distillation occurs. The volume of water that is removed was observed and distillation was continued until no further water was collected.

The contents of the flask are cooled, the beads filtered, washed in acetone and dried in hot air.

The final product has 12 to 15% moisture content, is in the form of beads of regular almost spherical shape that are hard and free flowing and dissolved readily in cold and hot water. The beads have a narrow size range of approximately 250 to 500 μ m and the product was substantially free of dust. The beads are insoluble and non-swelling in tap water but dissolved when exposed to water having pH 9.

Example 3

To demonstrate the effect of small differences in pH, beads were made by the process of Example 1 or Example 2 and contained 1% Carbolan Blue (a water soluble dye) and 10% china clay (particle size 2-5 μ m). The beads were exposed to an aqueous medium of gradually increasing pH.

The amount (%) released at different pH values was as follows:

pH	6.26	7.18	7.21	7.38	7.43	7.5
dye	4.5	14.62	18.76	73.06	85.74	100
clay	0	2.3	-	-	3.0	100

This demonstrates that the release of soluble materials can be controlled by pH adjustment but that swelling of the matrix may allow some release slightly below the pH value at which major release occurs, whereas the release of insoluble materials (such as pigments and cellular materials) can be controlled so that substantially total release occurs over a very narrow pH range (typically below 0.2 or 0.1 pH units) with substantially no release at lower pH values.

Example 4

The process of example 2 is repeated except that the copolymer emulsion is replaced by an equivalent amount of polymethacrylic acid as the 100% ammonium salt.

The final beads have the polymer mainly has the free acid polymer, especially near the surface. The beads dissolve rapidly in water when mixed into water with other detergent components.

As a comparison, when sodium polyacrylate is used in place of ammonium polyacrylate, the final beads have the polymer in the sodium form and they are less stable against loss of enzymic activity during storage, presumably because the polymer is more hydrophilic.

Claims

1. - A process of forming a particulate composition comprising particles comprising an active ingredient distributed substantially uniformly through a dried matrix comprising anionic polymeric material wholly or mainly in free acid form, wherein the amount of polymeric material in the particles is at least 0.5 times the weight of active ingredient and is at least 50% of the weight of the matrix, the polymeric material is soluble or swellable in water at a solubilising pH above 7, and the polymeric material at least in the outer surface of the matrix is substantially less soluble or less swellable in water at a pH below the solubilising pH, characterised in that the process comprises forming a dispersion in water immiscible liquid of aqueous particles containing a solution or dispersion of the active ingredient either in an aqueous solution of a salt of the polymer with a volatile amine or in an oil-in-water emulsion of the polymer wholly or mainly in free acid form, and subjecting the dispersion to azeotropic distillation and thereby forming the particles comprising the active ingredient distributed substantially uniformly through a dried matrix comprising the anionic polymeric material wholly or mainly in free acid form.
2. A process according to claim 1 comprising the preliminary step of dispersing or dissolving the active ingredient into a solution of the polymer or into an oil-in-water emulsion of the polymer.
3. A process according to claim 1 or claim 2 in which the dispersion in water immiscible liquid is formed by dispersing into the liquid a solution or dispersion of the active ingredient in an aqueous solution of the polymer with a volatile amine.
4. A process according to any of claims 1 to 3 in which the polymer is formed from ethylenically unsaturated monomer comprising carboxylic monomer and is present in the dispersion in water immiscible liquid as an aqueous solution of a salt with a volatile amine and the amine is volatilised

during the azeotroping whereby the polymer is present in the dried matrix mainly as free acid, at least in the outer surface of the matrix.

- 5 5. A process according to any preceding claim in which the polymer is formed of 50 to 100% by weight (meth) acrylic acid and 0 to 50% acrylamide.
- 10 6. A process according to any of claims 1 to 5 in which the polymer was made by oil-in-water emulsion polymerisation of a monomer blend comprising at least one ethylenically unsaturated anionic monomer and at least one ethylenically unsaturated non-ionic monomer, and the polymer is soluble or swellable in alkali.
- 15 7. A process according to any preceding claim in which the amount of polymer is at least 7 times the amount of active ingredient and the polymer is at least 90% by weight of the matrix.
- 20 8. A process according to claim 7 in which the amount of polymer is 15 to 50 times the amount of the active ingredient.
- 25 9. A process according to any preceding claim in which the active ingredient is selected from enzymes, fungi, spores, bacteria, cells and antibiotics.
- 30 10. A process according to any of claims 1 to 9 in which the particles have a size of below 10 μ m and are present as a stable dispersion in the water immiscible liquid.
- 35 11. A process according to any of claims 1 to 9 in which the particles are dry particles having a size of at least 30 μ m.
12. A process according to any of claims 1 to 9 in which the particles are dry beads having a size of 100 μ m to 2mm.
13. A process according to claim 11 or claim 12 in which the particles have a size of at least 30 μ m, the active ingredient is a pesticide that is to be effective in animal faeces, the matrix does not release the active ingredient while the particles are in the mouth or passing through the cow, but the polymer does swell or dissolve sufficient to release the active ingredient when the particles are exposed to ammonia in the faeces.
14. A process according to any of claims 1 to 12 in which the active ingredient is a detergent enzyme.

Patentansprüche

- 40 1. Verfahren zur Bildung einer teilchenförmigen Zusammensetzung, welche Teilchen umfaßt, die einen aktiven Bestandteil umfassen, der im wesentlichen gleichförmig innerhalb einer getrockneten Matrix verteilt ist, die anionisches polymeres Material vollständig oder vorwiegend in Form einer freien Säure umfaßt, wobei die Menge an polymerem Material in den Teilchen mindestens dem 0,5-fachen des Gewichts des aktiven Bestandteils entspricht und mindestens 50% des Gewichts der Matrix ausmacht, und das polymere Material in Wasser bei einem löslich machenden pH-Wert von über 7 löslich oder quellfähig ist, und wobei das polymere Material zumindest an der Außenoberfläche der Matrix in Wasser bei einem pH-Wert unterhalb des löslich machenden pH-Wertes wesentlich weniger löslich oder weniger quellfähig ist, dadurch gekennzeichnet, daß das Verfahren umfaßt: die Bildung einer Dispersion in einer mit Wasser nicht mischbaren Flüssigkeit von wässrigen Teilchen, die eine Lösung oder Dispersion des aktiven Bestandteils entweder als wässrige Lösung eines Salzes des Polymers mit einem flüchtigen Amin oder in einer Öl/Wasser-Emulsion des Polymers, vollständig oder hauptsächlich in Form einer freien Säure, enthält; und azeotrope Destillation der Dispersion, wobei die Teilchen gebildet werden, die den aktiven Bestandteil umfassen, der im wesentlichen gleichförmig innerhalb einer getrockneten Matrix verteilt ist, die das anionische polymere Material vollständig oder hauptsächlich in Form einer freien Säure umfaßt.
- 55 2. Verfahren nach Anspruch 1, welches den Vorbehandlungsschritt des Dispergierens oder Lösens des aktiven Bestandteiles in einer Lösung des Polymers oder in einer Öl/Wasser-Emulsion des Polymers

umfaßt.

3. Verfahren nach Anspruch 1 oder 2, worin die Dispersion in der mit Wasser nicht mischbaren Flüssigkeit durch Dispergieren in der Flüssigkeit einer Lösung oder Dispersion des aktiven Bestandteiles in einer wässrigen Lösung des Polymers mit einem flüchtigen Amin gebildet wird.
4. Verfahren nach einem der Ansprüche 1 bis 3, worin das Polymer aus einem ethylenisch ungesättigten Monomer gebildet wird, das einen Carboxylrest enthaltendes Monomer umfaßt und in der mit Wasser nicht mischbaren flüssigen Dispersion als eine wässrige Lösung eines Salzes mit einem flüchtigen Amin anwesend ist, und das Amin während der Azeotropen Destillation verdampft wird, wobei das Polymer in der getrockneten Matrix, zumindest in der Außenoberfläche der Matrix, hauptsächlich als freie Säure anwesend ist.
5. Verfahren nach einem der vorhergehenden Ansprüche, worin das Polymer aus 50 bis 100 Gew.-% (Meth)acrylsäure und 0 bis 50 Gew.-% Acrylamid gebildet wird.
6. Verfahren nach einem der Ansprüche 1 bis 5, worin das Polymer durch eine Öl-in-Wasser-Emulsionspolymerisation einer Monomermischung gebildet wurde, die mindestens ein ethylenisch ungesättigtes anionisches Monomer und mindestens ein ethylenisch ungesättigtes nicht-ionisches Monomer umfaßt, und das Polymer in Alkali löslich oder quellfähig ist.
7. Verfahren nach einem der vorhergehenden Ansprüche, worin die Menge des Polymers mindestens das 7-fache der Menge des aktiven Bestandteils ausmacht und das Polymer wenigstens 90% der Matrix beträgt.
8. Verfahren nach Anspruch 7, worin die Menge des Polymers das 15- bis 50-fache der Menge des aktiven Bestandteils ausmacht.
9. Verfahren nach einem der vorhergehenden Ansprüche, worin der aktive Bestandteil ausgewählt wird aus Enzymen, Pilzen, Sporen, Bakterien, Zellen und Antibiotika.
10. Verfahren nach einem der Ansprüche 1 bis 9, worin die Teilchen eine Größe von weniger als 10µm aufweisen und als eine stabile Dispersion in der mit Wasser nicht mischbaren Flüssigkeit vorliegen.
11. Verfahren nach einem der Ansprüche 1 bis 9, worin die Teilchen trockene Teilchen mit einer Größe von mindestens 30µm sind.
12. Verfahren nach einem der Ansprüche 1 bis 9, worin die Teilchen trockene Perlen mit einer Größe von 100µm bis 2mm sind.
13. Verfahren nach Anspruch 11 oder 12, worin die Teilchen eine Größe von mindestens 30µm haben, der aktive Bestandteil ein Schädlingsbekämpfungsmittel ist, das in Tierkot wirksam ist, die Matrix den aktiven Bestandteil nicht freisetzt, während die Teilchen im Maul sind oder die Kuh durchlaufen, jedoch das Polymer ausreichend quillt oder sich auflöst, um den aktiven Bestandteil freizusetzen, wenn die Teilchen Ammoniak oder Kot ausgesetzt werden.
14. Verfahren nach einem der Ansprüche 1 bis 12, worin der aktive Bestandteil ein Detergens-Enzym ist.

Revendications

1. Procédé de formation d'une composition particulière comprenant des particules contenant un ingrédient actif distribué sensiblement uniformément dans une matrice séchée comprenant une matière polymérique anionique totalement ou principalement sous forme d'acide libre, dans lequel la quantité de matière polymérique dans les particules représente au moins 0,5 fois le poids d'ingrédient actif et représente au moins 50% du poids de la matrice, la matière polymérique étant soluble ou gonflable dans l'eau à un pH de solubilisation supérieur à 7, et la matière polymérique, au moins dans la surface externe de la matrice, étant sensiblement moins soluble ou moins gonflable dans l'eau à un pH inférieur au pH de solubilisation, caractérisé en ce que le procédé comprend la formation d'une dispersion dans un liquide

immiscible à l'eau de particules aqueuses contenant une solution ou dispersion de l'ingrédient actif dans une solution aqueuse d'un sel du polymère et d'une amine volatile ou dans une émulsion huile-dans-l'eau du polymère totalement ou principalement sous forme d'acide libre, et la soumission de la dispersion à une distillation azéotropique pour former des particules comprenant l'ingrédient actif distribué sensiblement uniformément dans une matrice séchée comprenant la matière polymérique anionique totalement ou principalement sous forme d'acide libre.

2. Procédé selon la revendication 1, comprenant l'étape préliminaire consistant à disperser ou dissoudre l'ingrédient actif dans une solution du polymère ou dans une émulsion huile-dans-l'eau du polymère.
3. Procédé selon la revendication 1 ou la revendication 2, dans lequel la dispersion dans le liquide immiscible à l'eau est formée par dispersion dans le liquide d'une solution ou dispersion de l'ingrédient actif dans une solution aqueuse du polymère avec une amine volatile.
4. Procédé selon l'une quelconque des revendications 1 à 3, dans lequel le polymère est formé à partir d'un monomère éthyléniquement insaturé comprenant un monomère carboxylique et est présent dans la dispersion dans le liquide immiscible à l'eau sous forme d'une solution aqueuse d'un sel avec une amine volatile et l'amine est volatilisée au cours de la distillation azéotropique de sorte que le polymère est présent dans la matrice séchée principalement sous forme d'acide libre, au moins dans la surface externe de la matrice.
5. Procédé selon l'une quelconque des revendications précédentes, dans lequel le polymère est constitué de 50 à 100% en poids d'acide (méth)acrylique et de 0 à 50% d'acrylamide.
6. Procédé selon l'une quelconque des revendications 1 à 5, dans lequel le polymère a été préparé par polymérisation en émulsion huile-dans-l'eau d'un mélange de monomères comprenant au moins un monomère anionique éthyléniquement insaturé et au moins un monomère non ionique éthyléniquement insaturé, et le polymère est soluble ou gonflable dans les alcalis.
7. Procédé selon l'une quelconque des revendications précédentes, dans lequel la quantité de polymère représente au moins 7 fois la quantité d'ingrédient actif et le polymère constitue au moins 90% en poids de la matrice.
8. Procédé selon la revendication 7, dans lequel la quantité de polymère représente 15 à 50 fois la quantité d'ingrédient actif.
9. Procédé selon l'une quelconque des revendications précédentes, dans lequel l'ingrédient actif est choisi parmi les enzymes, les champignons, les spores, les bactéries, les cellules et les antibiotiques.
10. Procédé selon l'une quelconque des revendications 1 à 9, dans lequel les particules ont une taille inférieure à 10 μm et sont présentes sous forme d'une dispersion stable dans le liquide immiscible à l'eau.
11. Procédé selon l'une quelconque des revendications 1 à 9, dans lequel les particules sont des particules sèches d'une taille d'au moins 30 μm .
12. Procédé selon l'une quelconque des revendications 1 à 9, dans lequel les particules sont des perles sèches d'une taille de 100 μm à 2 mm.
13. Procédé selon la revendication 11 ou la revendication 12, dans lequel les particules ont une taille d'au moins 30 μm , l'ingrédient actif est un pesticide qui doit être efficace dans les matières fécales des animaux, la matrice ne libère pas l'ingrédient actif tandis que les particules sont dans la bouche ou traversent la vache, mais le polymère gonfle ou se dissout suffisamment pour libérer l'ingrédient actif lorsque les particules sont exposées à l'ammoniac dans les matières fécales.
14. Procédé selon l'une quelconque des revendications 1 à 12, dans lequel l'ingrédient actif est une enzyme détergente.